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Review

Neuropsychopharmacology of drug seeking: Insights from studies with second-order schedules of drug reinforcement☆

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Abstract

Second-order schedules of reinforcement model complex chains of responding for rewards such as food or drugs. Derived from studies of conditioned reinforcement, an important feature of these schedules is that responding is maintained by the response-dependent presentation of conditioned stimuli. They are thus well-suited to the study of the influences over drug seeking exerted by drug-associated stimuli. In the present review, we summarise studies investigating the neurobiology and neuropsychopharmacology of responding for cocaine under a second-order schedule of reinforcement. We conclude that limbic–striatal circuitries underlie drug seeking measured in this way. Emphasis is placed on potential interactions between structures within these subsystems by reviewing neuropsychopharmacological studies in which antagonists selective for either glutamate or dopamine receptors have been infused directly into limbic, cortical and striatal areas.

Keywords: Second-order schedules of reinforcement; Cocaine; Amygdala; Nucleus accumben; Dopamine; Glutamate

Contents

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1. Introduction

Drug addiction is characterised primarily by the harm caused to an individual due to uncontrolled continued use of the substance (American Psychiatric Association, 1994). Central to an understanding and treatment of addiction, thus, would be to define the ways in which drugs of abuse are continually used, despite efforts to stop. Several theoretical approaches have been developed to explain drug use, each with emphasis on an important, yet distinct, aspect of addiction. For example, one view (Koob and Le Moal, 2001) posits that through prolonged exposure to the drug, behavioural and neural adaptations occur (Solomon and Corbit, 1974) that 'reset' the organism's hedonic homeostasis specifically such that drug intake becomes dysregulated (allostasis). By comparison, the 'Incentive Sensitisation' theory (Robinson and Berridge, 1993) posits that intermittent exposure to drugs of abuse (Robinson and Becker, 1986) causes an increased response of the neural system underlying motivation to use drug (Berridge and Robinson, 1998) thereby leading to increased drug 'wanting' (Robinson and Berridge, 2002). The topic of other reviews (Shaham et al., 2003; Shalev et al., 2002), relapse models (de Wit and Stewart, 1981) with high predictive validity (Epstein and Preston, 2003) have provided insights into the mechanism by which re-exposure to drugs of abuse (Gerber and Stretch, 1975; Kalivas and McFarland, 2003; Stretch and Gerber, 1973), environmental stimuli (See, 2002) or stressors (Shaham et al., 1996) can induce relapse to drug use, even after prolonged drug withdrawal.

The focus of this review is on another aspect of drug addiction: the control over drug seeking by conditioned environmental stimuli (O'Brien et al., 1990; Stewart et al., 1984; Wikler, 1965). Specifically, we will focus on the use of second-order schedules of drug reinforcement (Arroyo et al., 1998; Everitt and Robbins, 2000; Goldberg et al., 1975) to define the neuropsychopharmacological mechanisms within limbic–cortical–striatal systems underlying the control over prolonged drug seeking by conditioned environmental stimuli.

Associative mechanisms are critical to the maintenance of everyday behaviour. In mature animals, few behaviours are reinforced immediately by primary reward such as food, sex or drugs; instead, environmental signals are necessary to shape behaviour (Holland, 1977). Contextual cues may induce behaviours or arouse expectancies (Dickinson, 1994; Tolman, 1949) that signal that a specific behaviour will be rewarded in that particular context (Bouton, 1993). Subsequently, responses are often reinforced by stimuli with conditioned reinforcing properties, such as money or praise (Williams, 1994). Further, many everyday activities are reinforced not only after a response, but at regular times of the day, such as eating. Indeed, eating happens at regular intervals following an appropriate set of integrated behaviours, each reinforced by conditioned environmental events, and aimed at procuring the goal. Similarly, an addict may be required to carry out a variety of acts to acquire and self-administer a drug of choice.

2. Second-order schedules of drug reinforcement

Second-order schedules of reinforcement are derived from studies of animal learning that model complex chains of responding, in which each step in the chain is reinforced by a conditioned reinforcer, that ultimately produces a primary reward (Kelleher, 1966). Under these schedules, the presentation of each conditioned stimulus not only reinforces instrumental behaviour, but also signals to the animal that a successive step in the chain has been completed, and the next step can be commenced (Ferster and Skinner, 1957). In adapting second-order schedules to drug addiction (Everitt and Robbins, 2000; Schindler et al., 2002), it was demonstrated that a number of addictive drugs can support robust responding under these schedules, including: morphine (Goldberg, 1976), phencyclidine (Carroll, 1985), pentobarbital (Johanson, 1982), heroin (Corrigall and Coen, 1989), cocaine (Goldberg, 1973), 'speedball' (Mello et al., 1995), buprenorphine (Mello et al., 1981), cannabis (Justinova et al., 2003) and nicotine (Goldberg et al., 1981). The ability of stimuli paired with a variety of drugs of abuse to support responding under second-order schedules of reinforcement suggests that this is a key aspect of drug addiction, namely, prolonged drug seeking behaviour (Everitt and Robbins, 2000; Goldberg et al., 1975; Katz, 1980). The additional demonstration that humans will learn to respond for cocaine (Panlilio et al., 2005), opioids (Lamb et al., 1991), marihuana (Mello and Mendelson, 1985) and alcohol (Mello et al., 1990) under second-order schedules within the laboratory suggests that this type of drug seeking is worthy of further pre-clinical investigation.

Under second-order schedules of reinforcement in rats, animals are initially trained to self-administer drug, with each infusion being paired with a conditioned environmental stimulus. It is during this stage when an association is formed between the self-administered intravenous drug infusion and the conditioned stimulus, typically a stimulus light above the response lever (Arroyo et al., 1998; Goldberg, 1973). After repeated pairings, this light is capable of maintaining responding on its own (i.e. animals will work for it), and it is this conditioned reinforcing property that ultimately maintains responding under second-order schedules. Rats may be initially required to make, for instance, 5 responses for the conditioned stimulus, with the 4th conditioned stimulus presentation leading to drug reward. The schedule is then gradually incremented such that rats are required to make an increasing number of responses for the light, with drug being available at regular intervals to reinforce ongoing responding. Generally, in the procedure we have used, rats are required ultimately to make 10 responses for each conditioned stimulus presentation, and the first conditioned stimulus presentation after every 15 min interval is reinforced by drug reward.

Fig. 1 provides a typical example of responding by a rat under this type of second-order schedule. An important feature is that the differential control over responding by the conditioned stimulus and the drug can be demonstrated (Goldberg et al., 1975). For instance, responding for the conditioned stimulus by individual rats reveals response patterns typical of the schedule of reinforcement in effect for the stimulus presentation (Goldberg and Tang, 1977; Wilson and Bowman, 2004), in this instance a stimulus is presented after every 10th response; thus, step-like patterns show a cumulative increase over time (Goldberg and Tang, 1977; Goldberg and Kelleher, 1976). In the example provided in Fig. 1, this is superimposed on a scalloped pattern of responding over time, typical of responding under interval schedules, as for the drug under this overall

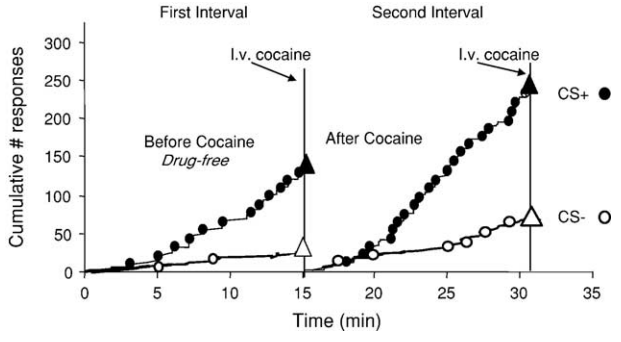

Fig. 1. Cumulative response record from a representative individual rat responding for cocaine under a second-order schedule of reinforcement. Scalloped responding was observed, characteristic of the interval schedule used for cocaine availability (cocaine infusion represented by triangle). Superimposed on these were the post-reinforcement pauses typical of responding under ratio schedules, in this study reinforced by presentation of the conditioned stimulus (circles). By comparison, responding for cocaine was not increased when a stimulus not paired with cocaine infusions was made available. Responding after self-administered cocaine was increased, reflecting the potentiation of conditioned reinforcement by the psychostimulant. Abbreviations: CS: conditioned stimulus; i.v.: intravenous.

second-order schedule. Removal of the conditioned stimulus, or replacing it with a light not paired with drug, reveals scalloped patterns of responding over the interval, demonstrating that animals are still responding for the drug but with much less vigour (Di Ciano and Everitt, 2003; Goldberg et al., 1981; Katz, 1979). However, removal of the drug reward results in a dramatic decrease in responding over days (Di Ciano and Everitt, 2001), though this extinction is slowed if the drug-associated conditioned reinforcer is also presented (Arroyo et al., 1998; Di Ciano and Everitt, 2002). Thus, under second-order schedules of reinforcement, it is the active drug seeking that is increased by the availability of conditioned reinforcers.

Following receipt of the first self-administered drug infusion, response rates increase (Barrett et al., 1981; Bond et al., 1975; Gonzalez and Goldberg, 1977; Katz, 1980) and this may reflect the impact of self-administered drug on the conditioned reinforcing properties of the conditioned stimulus paired with cocaine (Arroyo et al., 1998; Di Ciano and Everitt, 2003). As illustrated in Fig. 1, following cocaine infusions, responding in the subsequent 15 min is increased, typically by two-fold, but sometimes by much more. Responding after cocaine is still under the control of the drug-paired conditioned reinforcer, as demonstrated by step-like response patterns. Although drug seeking increases after cocaine self-administration even when a conditioned reinforcer is not available, responses are increased to a much greater extent in the presence of contingent presentations of the conditioned stimulus (Di Ciano and Everitt, 2003). This increase in responding is consistent with previous observations that psychostimulants can potentiate selectivity the conditioned reinforcing properties of stimuli previously paired with food or water rewards (Robbins, 1977).

Not only is the presentation of this brief conditioned stimulus previously paired with drug (Goldberg et al., 1979) necessary to maintain responding (Goldberg and Tang, 1977) it is also the contingency between the response and the conditioned stimulus that is important for responding under second-order schedules of reinforcement. Thus, unexpected presentations of the conditioned stimulus have no impact on ongoing drug seeking. By contrast, when permitted to make a response for the *same stimulus*, drug seeking is greatly increased (Di Ciano and Everitt, 2003). Reinstatement of drug seeking following extinction also depends upon response-dependent presentations of drug-associated stimuli (Deroche-Gamonet et al., 2002; Grimm et al., 2000). Thus, an understanding of the neural substrates of conditioned reinforcement, that is, the *response dependent* presentations of the conditioned stimulus, may be especially important to understanding the drug seeking that characterises addictive behaviour.

In summary, responding under second-order schedules of reinforcement is mediated by at least three motivational processes. First, it is controlled by drug reinforcement, as cocaine is available intermittently. Second, during these intervals, response rates are maintained by contingent presentations of the cocaine-associated conditioned reinforcer. During the first interval before cocaine is self-administered, responding is unaffected by the rate-altering and other

pharmacological effects of cocaine and thus truly reflects cocaine-seeking dependent on cocaine-paired conditioned reinforcers. Third, self-administered cocaine increases responding yet further (Arroyo et al., 1998; Di Ciano and Everitt, 2003) which reflects a potentiation of the conditioned reinforcing properties of the cocaine-associated stimulus by this self-administered psychostimulant (Everitt and Robbins, 2000).

3. Defining the neural systems of associative control over drug seeking

It is known that presentation of drug-paired conditioned stimuli to humans induces 'craving' and correlated characteristic patterns of brain activation in the temporal and frontal cortices (Childress et al., 1999; Grant et al., 1996). Further, these cortical areas are also activated following the presentation of heroin-paired stimuli (Gottfried et al., 2003), suggesting that these brain areas form part of a neural system important in conditioned influences on addiction, regardless of the specific drug with which the stimuli were paired. Indeed, different patterns of neural activity are observed in response to, as compared to conditioned anticipation of, drug (Breiter et al., 1997), suggesting that conditioned stimuli do more than just activate the same brain areas as the drugs themselves, through some simple associative mechanism. Instead, the involvement of limbic–cortical areas in associative mechanisms suggests that conditioned stimuli may induce drug seeking through interactions with the ventral striatum to which they project and are thereby modulated by the mesolimbic dopamine system, long associated with incentive motivation (Berridge and Robinson, 1998; Mogenson and Phillips, 1976; Stewart et al., 1984; White and Milner, 1992).

In extending this analysis of the neural systems involved in associative mechanisms that influence, and even induce, drug seeking in humans to experiments in animals, a number of different techniques can be used. A combination of lesion, inactivation, neuropsychopharmacological and in vivo neurochemical studies have been used to define the neural basis of drug seeking measured with second-order schedules. Lesions or temporary inactivations of brain areas can reveal the function of a particular neural structure, but lack the neurotransmitter selectivity of neurochemical and neuropharmacological approaches. Thus, direct infusion of drugs acting at specific receptors can provide a more detailed description of the precise neurotransmitters involved in the neural mechanisms underlying a given behaviour. Combined with knowledge about the distribution and connectivities of the neurons using these neurotransmitters, some understanding of the functional neuroanatomy of a specified behaviour can thereby be gained.

The present review is divided into two sections. First, experiments investigating the brain areas involved in responding for drugs under second-order schedules, using discrete lesions or inactivations, of limbic, cortical and striatal regions will be summarised. Specific hypotheses can thus be derived about the functional relationships between structures. In the second section, in an attempt to delineate the nature of such interactions, neuropsychopharmacological findings will be reviewed, in an attempt to define the neural systems that control drug seeking under second-order schedules of reinforcement.

4. Neurobiology of responding for drugs under second-order schedules of reinforcement

4.1. Ventral tegmental area

Consistent with findings from the studies mentioned above with humans, evidence shows that limbic–cortical ventral striatal systems mediate responding for drugs under second-order schedules of reinforcement and are modulated by the mesolimbic dopamine system having its cell bodies in the ventral tegmental area. Thus, inactivation of the ventral tegmental area resulted in decreased responding for cocaine under a second-order schedule of reinforcement (Di Ciano and Everitt, 2004b), suggesting that activation of dopamine transmission in the terminal domains of the mesolimbic dopamine system is an important component of conditioned stimulus-maintained drug seeking. The ventral tegmental dopamine neurons project to a number of structures, including the prefrontal cortex (medial, orbital, cingulate), amygdala and nucleus accumbens (Swanson, 1982). Each of these regions could therefore be the site at which ventral tegmental area inactivation has its functional consequences.

4.2. Basolateral amyglada

4.2.1. Cocaine

Lesions of the basolateral amygdala produced dramatic decreases in the *acquisition* of responding for cocaine under a second-order schedule of reinforcement (Whitelaw et al., 1996). However, inactivation of the basolateral amygdala with lidocaine had no effect on *established* responding for cocaine under a second-order schedule (Kantak et al., 2002a), while inactivation with intra-amygdala gamma-aminobutyric acid (GABA) receptor agonists had little effect (Di Ciano and Everitt, 2004b). However, it should be noted that dopamine receptor blockade in the basolateral amygdala did block responding for cocaine under a second-order schedule of reinforcement (Di Ciano and Everitt, 2004c), consistent with observations that inactivation of the basolateral amygdala blocked cue-induced reinstatement of cocaine seeking (Grimm and See, 2000). The possible reason for the difference between GABA agonist or local anaesthetic-induced inactivations and dopamine receptor antagonists infused into the amygdala is discussed further below.

4.2.2. Is heroin different?

Consistent with findings from studies with cocaine, inactivation of the basolateral amygdala with tetrodotoxin impaired cue-induced reinstatement of heroin seeking (Fuchs and See, 2002). By contrast, basolateral amygdala lesions did not impair the acquisition of heroin-seeking under a second-order schedule of reinforcement (Alderson et al., 2000). However, in this study it was also demonstrated that the heroin-associated conditioned stimulus had weak control over

responding and this may explain the absence of effect of basolateral amygdala lesions (Alderson et al., 2000). In addition, changes in response requirements for conditioned reinforcers produced more variable responding when the conditioned stimulus was paired with heroin than when it was paired with cocaine (Di Ciano and Everitt, 2003), suggesting that procedural variables may influence responding for heroin under second-order schedules more than for cocaine. Regardless of procedural considerations, it should be considered that cocaine and heroin may have different, if overlapping, neural substrates of reinforcement (Ettenberg et al., 1982), and it is therefore possible that they may also engage different mechanisms in the formation of environmental associations. In this regard, some differences are apparent between cocaine-conditioned and heroin-conditioned behaviours, in that it is known that cocaine conditioned effects in humans are almost always drug-like (O'Brien et al., 1992), while heroin conditioned behaviours can be either drug-like or drug-opposite (Wikler, 1965). Therefore, although the reasons for the differences between the neural substrates of cocaine and heroin seeking are unclear, it appears that the basolateral amygdala may be involved in the acquisition of responding for cocaine under second-order schedules of reinforcement, while its precise role in the associative influences over heroin seeking remain to be determined.

4.3. Nucleus accumbens

Original reports implicated the nucleus accumbens in cocaine reinforcement, as lesions of the *entire* nucleus accumbens abolished the acquisition of cocaine self-administration (Roberts et al., 1980). However, neuroanatomical evidence for structural heterogeneity in the nucleus accumbens (Zahm and Brog, 1992) has been supported by functional dissociations, with the shell, or medial accumbens, having been suggested to be more important for cocaine self-administration (Ikemoto et al., 2005) and the psychomotor stimulant effects of cocaine (Ito et al., 2004). Lesions of the nucleus accumbens core by contrast had little or no effect on cocaine self-administration, but markedly attenuated the acquisition of responding for cocaine under a second-order schedule of reinforcement, while lesions of the nucleus accumbens shell had no effect (Ito et al., 2004). These data suggest a role for the core subregion in associative influences over drug seeking.

Similarly, when the nucleus accumbens core was inactivated after *acquisition* of cocaine self-administration under a second-order schedule of reinforcement, responding was decreased (Di Ciano and Everitt, 2004b). In addition, scalloped response patterns for the drug were still evident following inactivations of the nucleus accumbens core, suggesting that cocaine reinforcement was unaffected (Di Ciano and Everitt, 2004b). Thus, decreases in responding following inactivation reflected a decrease in response rates maintained by the conditioned reinforcer. This view is supported by the additional finding that, following lesions of the nucleus accumbens core, rats were insensitive to omission of the conditioned stimulus, suggesting that the conditioned reinforcer was no longer maintaining responding (Fattore et al., 2002). Thus, the nucleus accumbens core seems important for responding for cocaine under second-order schedules by mediating conditioned reinforcement.

4.4. Prefrontal cortex

4.4.1. Orbitofrontal cortex

The prefrontal cortex is a heterogeneous structure with different subregions believed to be specialised for a particular function (Dalley et al., 2005). With respect to conditioned behaviours, the orbitofrontal cortex has been implicated in the formation of associations between stimuli and rewards (Gallagher et al., 1999; Rolls, 2000) and in appropriately directing behaviours towards these conditioned incentives (Bohn et al., 2003; Schoenbaum et al., 2003). Thus, it is not surprising that lesions of the orbitofrontal cortex disrupted the acquisition of responding for cocaine under a second-order schedule of reinforcement (Hutcheson and Everitt, 2003). Further, break points for cocaine under progressive ratio schedules were unaltered following lesions of the orbitofrontal cortex suggesting that the effect of orbitofrontal cortex lesions was selective to the associative control over drug seeking, and not to some aspect of drug reinforcement (Hutcheson and Everitt, 2003).

4.4.2. Medial prefrontal cortex

Based on studies of relapse to drug seeking, the medial prefrontal cortex, in the region of the prelimbic or cingulate cortex, has been suggested to be important for drug seeking mediated by all types of conditioned stimuli (Kalivas and McFarland, 2003). This hypothesis has merit given the hypothesised function of the prelimbic cortex in contingency learning (Corbit and Balleine, 2003; Dalley et al., 2004; Killcross and Coutureau, 2003) and the cingulate cortex in discriminative control over behaviour (Bussey et al., 1996). However, lesions of the medial prefrontal cortex did not impair the acquisition of responding under a second-order schedule of food reinforcement suggesting that the medial prefrontal cortex is not involved in conditioned reinforcement (Pears et al., 2003). Further, excitotoxic lesions of the medial prefrontal cortex not only facilitated the acquisition of, and responding for, low doses of cocaine, but also resulted in higher rates and disrupted patterns of responding compared to controls, when a second-order schedule of reinforcement was introduced (Weissenborn et al., 1997). These results suggest that the medial prefrontal cortex may not be involved in the maintenance of drug seeking by drug-associated conditioned reinforcers, and its precise role in drug seeking thus merits further consideration.

4.5. Summary

Fig. 2 presents a summary of findings of lesions or inactivations to brain areas on responding for drugs, primarily cocaine, under a second-order schedule of reinforcement. It

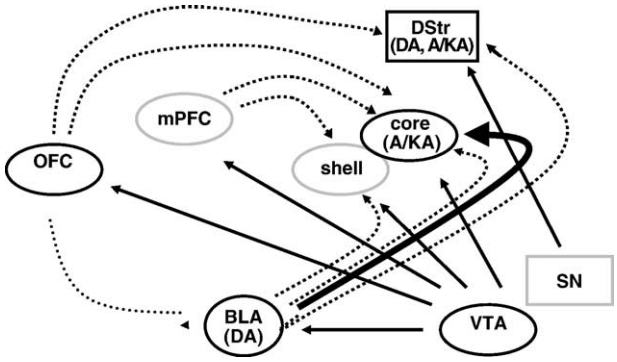

Fig. 2. Simplified diagram of interactions between the limbic–cortical and striatal regions in which lesions or inactivation abolished (dark circles), or had no effect (grey circles), on responding for cocaine under a second-order schedule of reinforcement (squares, not yet tested). Solid lines represent dopaminergic projections, while stippled lines are glutamatergic. DA and A/KA: represent areas where direct infusion of dopamine receptor, or AMPA/kainate receptor, antagonists, respectively, decreased responding for cocaine under a second-order schedule of reinforcement. Thick lines represent the system believed to be important in at least one aspect of responding for cocaine under a second-order schedule of reinforcement. Abbreviations: VTA: ventral tegmental area; SN: substantia nigra; DStr: dorsal striatum; mPFC: medial prefrontal cortex, OFC: orbitofrontal cortex; BLA: basolateral amygdala; A/KA: AMPA/kainate; DA: dopamine; core and shell: subregions of the nucleus accumbens.

should be noted that the orbitofrontal cortex has only been tested during acquisition, while inactivations of the basolateral amygdala had no (Kantak et al., 2002a), or little (Di Ciano and Everitt, 2004b), effect on *established* responding for cocaine under a second-order schedule of reinforcement. Based on these connectivities, we further investigated the effects of infusion of dopamine and glutamate receptor antagonists into these structures on responding for cocaine under a second-order schedule of reinforcement. The basic logic of these studies was that antagonism of a certain receptor could reveal systems-level functions. For example, an effect of dopamine receptor antagonists in specific terminal regions of the ventral tegmental area projection (e.g. the nucleus accumbens core or basolateral amygdala) would indicate that this is the locus of the effect of ventral tegmental area cell inactivation (Di Ciano and Everitt, 2004b) on responding for drug under a second-order schedule of reinforcement.

5. Neuropsychopharmacology of responding for drugs under second-order schedules of reinforcement

Traditional motivation theory ascribes a necessary role of the mesolimbic dopamine system in goal-directed behaviours (Beninger, 1983; Mogenson and Phillips, 1976; Phillips et al., 1991; White and Milner, 1992; Wise, 1978) and the ability of drug-paired conditioned stimuli to induce drug seeking responses (Robinson and Berridge, 1993; Stewart et al., 1984). Thus, understanding the neuropsychopharmacology of responding for cocaine under second-order schedules of reinforcement is important, as it can reveal the functional neural systems involved in associative control over drug seeking. In a series of studies, we have investigated the possible neurochemical mechanisms within limbic–cortical–striatal systems that underlie drug seeking under second-order schedules of reinforcement, focusing on dopamine and glutamate, which are major neurotransmitters in limbic–cortico–striatal systems. Dopamine and glutamate receptor antagonists have been infused into both cortical and striatal sites in order to define systems level interactions between component structures within these cortico-striatal networks.

5.1. Nucleus accumbens

In our first study of this type, infusion of glutamate receptor antagonists directly into the nucleus accumbens revealed pharmacologically and anatomically dissociable contributions of the core and shell subregions to responding for cocaine under a second-order schedule of reinforcement. Thus, in our initial investigations, we infused ionotropic glutamate receptor antagonists selective for either AMPA (alpha-Amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid hydrate)/kainate or *N*-methyl-D-aspartate (NMDA) receptors into the nucleus accumbens core or shell subregions.

5.1.1. Nucleus accumbens core

When infused directly into the nucleus accumbens core, the highly selective, water-soluble AMPA/kainate receptor antagonist, LY293558, dose-dependently decreased responding for cocaine under a second-order schedule of reinforcement (Di Ciano and Everitt, 2001). Further, this attenuation of responding persisted over all intervals of drug seeking; that is, both before and after self-administered cocaine. This is an important observation when considered with respect to the various processes maintaining responding under second-order schedules. That is, during the first interval, responding for drug is maintained by the conditioned reinforcer, while after self-administered cocaine, responding also reflects the pharmacological actions of the drug on responding and on conditioned reinforcement. Infusion of AMPA/kainate receptor antagonists produced the same relative decrease in responding both before and after cocaine, thus the potentiation in responding was still evident after cocaine, but on a lower baseline. This suggests that AMPA/kainate receptor antagonists infused into the nucleus accumbens core did not block the reinforcing or other pharmacological effects of cocaine, emphasising that the impact of AMPA/kainate receptor antagonism is on a process common to both intervals, namely, conditioned reinforcement (Di Ciano and Everitt, 2001).

The effects of AMPA/kainate receptor antagonists were not only to decrease responding for the conditioned reinforcer, but also to increase the number of responses observed on the inactive lever on which presses had no programmed consequences. This suggests that AMPA/kainate receptor blockade within the nucleus accumbens core cannot be explained simply by any change in motor activity, as the direction of change in responding on the two levers was in opposite directions. Thus, it was concluded that the effects of AMPA/kainate receptor antagonism was on some aspect of discriminative control over responding maintained by conditioned reinforcers. This is consistent with our similar observations that

infusion of AMPA/kainate receptor antagonists into the nucleus accumbens core also decreased conditioned approach to a conditioned stimulus predictive of food, while increasing approaches to an unpaired conditioned stimulus (Di Ciano et al., 2001b).

By contrast to glutamatergic receptor antagonists, infusion of the non-selective dopamine receptor antagonist alpha-flupenthixol into the nucleus accumbens core had no effect on responding for cocaine under a second-order schedule of reinforcement (Di Ciano and Everitt, 2004c). Similarly, results from in vivo studies have demonstrated that dopamine efflux is not increased during responding in extinction with conditioned reinforcers (Neisewander et al., 1996), cue-induced reinstatement of responding (Di Ciano et al., 2001a) or during responding for cocaine under a second-order schedule of reinforcement (Ito et al., 2000). At first glance, this may seem inconsistent with hypotheses that dopamine in the nucleus accumbens is required for non-specific, motoric (Carey, 1983) or effort-based (Salamone, 1994) aspects of behaviour. However, what these data suggest instead is that dopamine in the nucleus accumbens core is involved in a very specific aspect of behaviour and is probably not necessary for drug seeking maintained by conditioned reinforcers.

5.1.2. Nucleus accumbens shell

Reflecting the anatomical and functional heterogeneity of the nucleus accumbens core and shell subregions, as revealed by lesion studies (Ito et al., 2004), infusion of glutamatergic receptor antagonists into the nucleus accumbens shell had no effect on responding for cocaine under a second-order schedule of reinforcement (Di Ciano and Everitt, 2001).

5.2. Function of nucleus accumbens

The findings of these studies suggest a necessary role of the nucleus accumbens core in conditioned reinforcement mediated by AMPA/kainate glutamate receptors. These effects are presumably via interaction with glutamatergic afferents to the nucleus accumbens core, arising from limbic–cortical structures. The functional importance of these findings, then, with respect to instrumental responding for drug-paired conditioned stimuli, suggests that the nucleus accumbens core is ideally situated as a 'limbic-motor' interface integrating limbic motivational information and the selection of striatal behavioural responses (Mogenson et al., 1980).

It has been suggested that glutamate receptors in the nucleus accumbens are necessary for drug seeking, especially relapse, via interactions with the medial prefrontal cortex (Kalivas et al., 2005). By contrast, the limbic afferents important in mediating drug seeking under second-order schedules of reinforcement through interaction with the nucleus accumbens core remain to be determined, but our studies have suggested that this may be via the basolateral amygdala (Di Ciano and Everitt, 2004c). This will be discussed further below.

5.3. Basolateral amygdala

By contrast to its lack of effect when infused into the nucleus accumbens core, infusion of the non-selective dopamine receptor antagonist alpha-flupenthixol into the basolateral amygdala markedly decreased responding for cocaine under a second-order schedule of reinforcement (Di Ciano and Everitt, 2004c). This suggests that the impact of general inactivation of the ventral tegmental area on this behaviour is (Di Ciano and Everitt, 2004b), at least in part, mediated by reduced dopamine efflux in the basolateral amygdala. Further, we have demonstrated that the highly selective dopamine D3 receptor antagonist, SB-277011-A (Reavill et al., 2000), which decreases cocaine seeking when given systemically (Heidbreder et al., 2005; Le Foll et al., 2005), also decreased responding under a second-order schedule when infused directly into the basolateral amygdala (Di Ciano et al., submitted for publication). Dopamine D3 receptors are relatively localised to limbic–cortical areas, the nucleus accumbens and the amygdala, especially within the basolateral amygdala (Bouthenet et al., 1991; Gurevich and Joyce, 1999; Heidbreder et al., 2005; Suzuki et al., 1998) and thus, D3 receptor mediated dopamine transmission may be particularly involved with conditioned reinforcing influences on drug seeking.

By contrast, as mentioned in the above sections, GABA receptor agonist-induced inactivation of the basolateral amygdala had no effect on well-established responding for cocaine under second-order schedules of reinforcement (Di Ciano and Everitt, 2004b). However, it should be noted that the effect of GABA receptor mediated inactivation might not produce the same neuronal changes as direct antagonism of other transmitter receptors in the same area. For instance, spared function following inactivation may reflect compensatory changes in other brain areas, or the contribution of other structures to this behaviour (Coutureau and Killcross, 2003; Yin et al., 2004). Similarly, inactivation by blockade of sodium channels with tetrodotoxin or lidocaine (Grimm and See, 2000), or stimulation of inhibitory GABA receptors with baclofen and muscimol (McFarland and Kalivas, 2001), may produce different local effects on fibres of passage or local circuits, from dopamine receptor antagonists. Differences between findings with temporary inactivations or receptor antagonists are also considered in other reviews within this present issue (Bossert et al., 2005—this issue; Schmidt et al., 2005—this issue). Whatever the explanation, it is apparent that dopamine receptors within the basolateral amygdala are important in maintaining well-established drug seeking under second-order schedules of reinforcement, that is, drug seeking dependent on the presentation of conditioned reinforcers.

By contrast to dopamine receptor blockade, infusion of ionotropic AMPA/kainate glutamate receptor antagonists into the basolateral amygdala had no effect on responding for cocaine under a second-order schedule of reinforcement (Di Ciano and Everitt, 2004c). Taken together with the findings that dopamine receptor antagonists were effective, it

can be concluded that it is the mesolimbic projections from the ventral tegmental area to the basolateral amygdala that are especially involved in the maintenance of responding for cocaine under second-order schedules of reinforcement.

5.4. Dorsal striatum

Although no lesion studies have been conducted to investigate the involvement of the dorsal striatum in mediating responding for cocaine under second-order schedules of reinforcement (but see: Kantak et al. (2002b) with discriminative stimuli), converging evidence warrants further investigation of its neuropsychopharmacology with respect to the control over drug seeking. Thus, infusion of dopamine receptor antagonists into the anterior dorsal lateral striatum dose-dependently decreased well-established responding for cocaine under a second-order schedule of reinforcement (Vanderschuren et al., 2005). This is consistent with observations that dopamine efflux was increased in the dorsal striatum while rats were responding for a conditioned reinforcer (Ito et al., 2002). By contrast to the basolateral amygdala and nucleus accumbens shell or core, not only did dopamine receptor antagonists block this behaviour, but glutamate receptor antagonists of the AMPA/kainate receptor subtype did so, too (Vanderschuren et al., 2005).

These findings suggest that the dorsal lateral striatum may mediate some of the control over responding for cocaine under a second-order schedule of reinforcement. Although dopaminergic lesions of the dorsal striatum did not impair the *acquisition* of responding with conditioned reinforcement (Taylor and Robbins, 1986), infusion of amphetamine into this area potentiated conditioned reinforcement (Kelley and Delfs, 1991), suggesting that it may be important once conditioned reinforcement is established. Further, it was found that dopamine efflux was increased in the dorsal striatum during a sign-tracking task (Phillips et al., 1993), believed to reflect a reflexive type of approach response (Williams and Williams, 1969). Together, these studies all implicate the dorsal striatum in habitual forms of responding (White, 1996; Yin et al., 2004), which may be related to the prolonged experience of responding with conditioned reinforcement (Di Ciano and Everitt, 2004a). The mechanism by which the dorsal striatum may mediate this information remains speculative, but anatomical feedback from the nucleus accumbens to the cell bodies in the ventral tegmental area and substantia nigra may provided an important mechanism (Haber et al., 2000).

5.5. Summary

Fig. 2 also summarises the findings discussed above of the effects of infusion of either dopamine, or glutamate, receptor antagonists into limbic–striatal regions on responding for cocaine under second-order schedules of reinforcement. After inspection of Fig. 2, several features are noteworthy: 1) different terminal regions are affected differentially by antagonists, by dopamine and glutamate receptor antagonists, and 2) the involvement of each neural structure is via different (combinations of) neurotransmitter receptor subtypes. Thus, in summary, it seems that the nucleus accumbens core, via interactions with limbic afferents, is important for cocaine-seeking under a second-order schedule of reinforcement. Further, it can also be concluded that the likely terminal region of the mesolimbic dopamine system mediating conditioned reinforcement may be the basolateral amygdala. In addition, dopaminergic mechanisms in the dorsal striatum are also important, perhaps forming part of a parallel neural system, modulated by the nigrostriatal dopamine system, that is recruited once the response has become well-established. These possibilities are discussed further below.

6. Neural systems of drug seeking

6.1. Responding for cocaine under second-order schedules of reinforcement is mediated by interactions between the nucleus accumbens and basolateral amygdala

Based on the findings summarised above, we conducted a further study to investigate a possible interaction between the dopaminergic innervation of the basolateral amygdala and its glutamatergic afferents to the nucleus accumbens core in the control over cocaine seeking (Di Ciano and Everitt, 2004c). The procedure used was a modified disconnection procedure that is based on the logic that if a brain system is involved in a given behaviour, then it is required to be intact on both sides of the brain. Thus, unilateral damage to the two nuclei in a given system controlling a behaviour would disrupt the behaviour if the unilateral damage was on opposite sides of the brain, thus functionally disconnecting the neural system within which they are embedded.

The disconnection procedure has been used in the past to demonstrate that disconnection of the basolateral amygdala and nucleus accumbens core attenuated conditioned place preference (Everitt et al., 1991) and that disconnection of the anterior cingulate cortex and nucleus accumbens disrupted Pavlovian conditioned approach (Parkinson et al., 2000a). Further, disconnection of the basolateral amygdala and dorsal striatum (Han et al., 1997), or the central amygdala and substantia nigra (Lee et al., 2005b) revealed functions of other cortical–striatal sub-circuits underlying appetitive Pavlovian conditioned orienting that may involve a central amygdala-substantia nigra-dorsal striatum pathway (Lee et al., 2005b).

A neuropharmacological disconnection was used to probe the functional relationship between AMPA/kainate receptors in the nucleus accumbens core and dopamine-dependent mechanisms in the basolateral amygdala in the control over responding for cocaine under a second-order schedule of reinforcement. Thus, unilateral blockade of AMPA/kainate receptors in the nucleus accumbens core with combined simultaneous blockade of dopamine receptors in the contralateral basolateral amygdala was predicted to attenuate responding for cocaine under a second-order schedule of reinforcement as effectively as blockade of these receptors bilaterally in either structure alone. Indeed, the results revealed a marked reduction in cocaine seeking following this disconnection, whereas unilateral infusion of the drugs into either the basolateral amygdala or

nucleus accumbens core alone was completely without effect. Thus, these data strongly indicate the functional importance of a serial link between dopamine transmission in the basolateral amygdala and its glutamatergic projections to the nucleus accumbens core in cocaine seeking (Di Ciano and Everitt, 2004c).

6.2. Other systems

In realising even the 'simplest' behaviour within an operant chamber, a number of different components can be engaged. For instance, through predictive pairings, a light can signal availability of a food reward and thus induce an approach response to a food cup. Thus, the light must induce, amongst others, an orienting response and an approach response (Holland, 1977). This distinction is relevant here as disconnection studies suggest that different neural circuitries may operate to control these various aspects of behaviour. For example, evidence suggests that an amygdala–dorsal striatum-dependent system may control conditioned orienting (Lee et al., 2005b), while a cingulate cortex–accumbens system underlies conditioned approach (Parkinson et al., 2000b). Both systems are required for the acquisition and performance of even this relatively 'simple' behaviour of obtaining reward from a food cup that is signalled by a stimulus signalling its availability.

Future studies will need to address the exact functioning of different cortico-striatal systems in the orchestrated control of goal-directed behaviour relevant to addiction (Berridge and Robinson, 2003). Thus, an important function of the medial prefrontal cortex–accumbens interactions has been ascribed to the reinstatement of drug seeking (Kalivas et al., 2005). To date, we have begun to define the critical role of basolateral amygdala–nucleus accumbens interactions (Di Ciano and Everitt, 2004c). Further, the dorsal striatum clearly plays an important role in well-established cocaine seeking (Ito et al., 2004; Vanderschuren et al., 2005), either through interactions with the basolateral amygdala, or in mediating a parallel process that may be related to well-established aspects of drug addiction (White, 1996). In this regard, it has recently been demonstrated that the nucleus accumbens regulates the balance between contextual and cognitive inputs from the hippocampus and medial prefrontal cortex, respectively (Goto and Grace, 2005). Similarly, different responses may converge on the striatum to control drug seeking. Future studies will need to parse and define the various aspects of behavioural control over drug seeking and the neuroanatomical and neuropsychopharmacological systems underlying them.

6.3. Clinical implications

Second-order schedules of drug reinforcement provide an animal model of prolonged drug seeking under the control of environmental contingencies for drug-associated conditioned stimuli. They may model some of the qualities of drug seeking by humans that make procuring drug a persistent goal and relapse to drug use in the presence of conditioned stimuli difficult to resist. It is thus that they may gain some of their pre-clinical utility (Backstrom and Hyytia, 2003; Czoty et al., 2002; Dole et al., 1966; Howell and Byrd, 1995; Kantak et al., 2000; Khroyan et al., 2000; Lee et al., 2005a, 2004; Mello et al., 1983; Mello and Negus, 1998; Platt et al., 2003, 2001). Second-order schedules of reinforcement may therefore provide a complementary approach to the study of drug seeking using extinction-relapse studies that have predictive validity in pre-clinical screening (Epstein and Preston, 2003).

The neuropsychopharmacological studies reviewed here may therefore provide clues to the development of novel treatments for drug addiction. The findings from these studies suggest, for example, that drugs that target dopamine receptors in the basolateral amygdala may be useful in the prevention of drug seeking. Indeed, we have demonstrated that systemic pre-treatment with a D3 selective dopamine receptor antagonist, SB-277011-A, decreased responding for cocaine under a second-order schedule of reinforcement (Di Ciano et al., 2003) and that this effect depends upon dopamine D3 receptor antagonism in the basolateral amygdala but not other D3 receptor-rich areas such as the nucleus accumbens shell or dorsal striatum (Di Ciano et al., submitted for publication). Such treatments may prove effective in the treatment of addiction not because they antagonise, or substitute for, the effects of self-administered drugs such as cocaine, but because they may promote abstinence by diminishing the impact of drug-associated conditioned reinforcers on abstinence, drug seeking and relapse.

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